

REMARKS/ARGUMENTS

Applicants acknowledge receipt of the Office Action mailed from the United States Patent Office on July 17, 2006. Claims 1, 3, 14-16, 25-35, 37, 40, 46-50, 52-54, 56, 58, 66, and 68 are pending in the application. Of these the Examiner states that claims 15-16, 30-35, 37, 40, 46-48, 50, 52-54, 58 and 68 are deemed allowable, but objected to for being dependent upon a rejected base claim. Claims 4-13, 17-24, 36, 38-39, 41-45, 51, 55, 57, 59-65, 67, and 69-77 were previously withdrawn, but are dependent upon claim 1. Thus, applicants respectfully request rejoinder upon allowance of claim 1.

Amendments and new claims

Claim 1 has been amended for clarification. Claims 138 and 139 have been added. Support for new claims 138 and 139 can be found in the specification and claims, for example, claim 49; and the definitions on page 9, line 23 through page 10, line 9. Support for the amendment to claim 1 specifying a separate reporter can be found in the specification and claims, for example, the paragraph starting on page 21 of the specification, entitled "Library of Complexes"; page 13, "General Screening Methods", line 25, which states "each complex comprising at least a compound and a reporter"; and page 22, lines 1-6. Support for the amendment specifying that the transport proteins are "expressed on the cell surface" can be found in the claims and specification, for example claim 1 and the "General Screening Methods" on page 13 describe "contacting the population of cells with a plurality of complexes", and Examples 2 and 3 which describe methods involving three types of transporters expressed on the cell surface. Support for the amendment specifying that the complexes can be simultaneously screened can be found in the specification and claims, including claim 1, page 18 which discusses multiplexed methods, and Example 2.

Summary of the Examiner Interview

Applicants would like to thank the Examiner for the telephonic interview on October 12, 2006. During the interview, clarifying amendments to claim 1 were discussed. The Examiner

stated that while the amendments would be likely to facilitate prosecution, that prosecution on the merits is closed and they could not be entered without the filing of an RCE.

Rejection under 35 U.S.C. §102(b)

Claims 1, 3, 14, 25-29, 49, 56 and 66 were rejected as being anticipated by Swanson et al. (Swanson, S.J., et al. *The Plant Cell*, May 1998, 10, 685-698) as evidenced by Ozkan et al. (Ozkan et al. *Biochim. Biophys. Acta*. 2002, 1572, 143-148).

The examiner maintained the previous rejection and stated that the arguments made in the response to the January 19, 2006 were not deemed persuasive for the following reasons:

A. "The features upon which applicant relies (e.g., substrate-reporter-quencher) are not recited in the rejected claim(s)." and further that "the claim does not read "(a) providing a library comprising different complexes, each complex comprising a substrate and a reporter", nor does the claim read "(a) providing a library comprising different complexes, each complex comprising a compound that cannot function as a quencher and a reporter." Therefore, Applicants' arguments are not commensurate in scope with the claims." Page 6, last paragraph of the office action.

B. The Examiner also states that "again, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., "extracellular contact) are not recited in the rejected claim(s)." Page 7, last paragraph of the office action.

C. The Examiner maintained that Swanson et al. disclose the use of a library of fluorescent conjugates in screening and/or characterizing two forms of vacuoles, protein storage and secondary vacuoles. The examiner specifically refers to BCECF-AM and ZFR-CMAC-GS in the abstract and Table 1 of Swanson et al. as examples of the complexes used to identify the vacuole as a secondary or a protein storage vacuole.

Claim 1 has been amended as follows:

1. (currently amended) A method of screening for a substrate to a carrier-type transport protein expressed on the plasma membrane of the cell surface, comprising:
 - (a) providing a library comprising different complexes, each complex comprising a compound and a separate reporter, the compound varying between different complexes;
 - (b) providing a population of cells, one or more of which expresses one or more carrier-type transport proteins on the plasma membrane of the cell surface;
 - (c) contacting the population of cells with a plurality of complexes from the library simultaneously; and
 - (d) detecting a signal from the reporter of a complex while internalized within a cell, wherein the reporter preferentially generates the signal once the reporter is internalized within the cell rather than from complexes binding to the surface of the cell, the signal thus providing an indication that a complex whose reporter generated the signal comprises a compound that is a substrate for a carrier-type transport protein expressed on the plasma membrane of the cell surface.
- provided that if the reporter comprises a fluorophore, the complex comprises a compound, a fluorophore and a quencher, and the fluorophore is linked to the a quencher by a linker susceptible to cleavage within the cell, whereby the quencher quenches fluorescence from the fluorophore outside the cell and is cleaved from the fluorophore within the cell after the complex is internalized within the cell, whereby the reporter preferentially generates the signal once internalized within the cell.

Swanson et al. discusses the use of a number of fluorescent compounds in screening and/or characterizing two forms of vacuoles, protein storage and secondary vacuoles. The compounds are all tested separately. Table 1 of Swanson et al. sets out all of the compounds used for characterization of vacuoles. The compounds are listed in groups by the location of fluorescence (cytoplasm and/or vacuole). All of the compounds used were fluorescent compounds. In most cases, they were only fluorescent reporters. One was a fluorescent reporter-quencher complex (BCECF-AM) and only one could arguably be called a fluorescent reporter-quencher-substrate complex (ZFR-CMAC-GS) because a glutathione (GS) substrate was added intracellularly.

In order to be an anticipatory reference, the single reference cited by the Office must disclose each and every element of the claims. *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81 (Fed. Cir. 1986).

Swanson et al. does not disclose all of the claim elements for the following reasons.

1. Swanson et al. does not teach or disclose the step of "providing a library comprising different complexes, each complex comprising a separate compound and a reporter, the compound varying between different complexes;" because arguably only one complex as claimed is discussed in Swanson et al. and this complex is not even produced extracellularly.

All of the reporters discussed in Swanson et al. are fluorophores (see Table 1 for a summary). For this reason, to fit the definition of a complex as claimed, Swanson et al would need to disclose a test compound-reporter-quencher complex in which the test compound and the reporter are separate. The examiner specifically refers to two complexes that are disclosed by Swanson et al., BCECF-AM and ZFR-CMAC-GS and states that these complexes constitute a library. However, in fact BCECF-AM is not a complex as defined in the claims because it does not include a test compound. BCECF-AM is simply a reporter/quencher complex. Assuming arguendo that ZFR-CMAC-GS does fit the definition of a complex, it is the only complex disclosed in Swanson et al. as claimed. The rest of the fluorophores are presented in Table 1 and are simply fluorophores. They do not contain a separate test compound and reporter. Therefore, Swanson et al. at most discuss one complex and does not provide a "library comprising different complexes."

2. Swanson et al. does not teach the simultaneous screening of test compounds

The presently amended claims clarify that the library allows "simultaneous" screening of the complexes as claimed. This can be seen throughout the specification and, for example, on page 14 which discusses multiplexed methods that allow for simultaneously screening multiple different complexes on the same cells.

The compounds described in Swanson et al. are each tested separately on the cells. Swanson does not disclose the use of "libraries" because a library is a collection of compounds with a unifying feature and the members of the library are capable of being analyzed

simultaneously. The test compounds used in Swanson are not analyzed simultaneously and nor are they capable of being analyzed simultaneously. One of skill in the art of fluorescence detection would have identified that the fluorophores used in Swanson could not be used simultaneously. This is because each of the fluorophores has very different excitation and emission wavelengths. It would not be possible to measure the different fluorophores at the same time or even quickly enough that each of the different fluorophores could be detected. Further, because there would be a complicated mixture of fluorophores with different emission and excitation wavelengths, it is likely that many would be quenched.

3. Swanson et al. does not teach or disclose the screening of carrier-type transporter proteins expressed on the cell membrane.

None of the test compounds that are used in Swanson et al. are transported into the cell by carrier proteins. The fluorescent transporters in Swanson et al. are loaded into the cells noninvasively, using microinjection or acid loading (see page 690, column 1, lines 7 and 8).

Further, the purpose of the method of Swanson is to identify the type of transport into vacuoles and would only identify intracellularly expressed transporters.

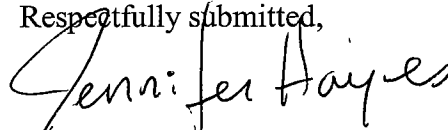
For the above reasons, Swanson et al. does not disclose all of the claim elements and Swanson et al. does not anticipate the claimed invention.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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